C3

59. An isolated nucleic acid comprising the cDNA insert of the vector deposited as ATCC accession number 209466.

REMARKS

Claims 1-9 are pending and are the subject of the present office action. Claims 1, 2 and 9 have been amended, and Claims 27-59 have been added, as shown above. Support for the amendments and added claims can be found on at least pages 7, 8, 10, 11, 14, 15, 40-42, and 48-51 of the specification. It is believed that no new matter is thereby introduced. A clean copy of now pending claims 1-9 and 27-59 is attached to this Amendment as Attachment A.

Each of the rejections set forth in the office action is addressed below.

Section 112 Rejections

Claims 1-9 were rejected under Section 112, second paragraph, as being indefinite. Claims 1 and 2 have been amended, as shown above, and it is believed that these amendments overcome the Examiner's rejection based on indefiniteness.

Claims 1 and 3-8 were rejected under Section 112, first paragraph, as containing subject matter which was not adequately described in the specification. Applicants respectfully disagree. The disclosure in Applicants' specification clearly provides description of various embodiments of DNA19355 polypeptides and encoding DNA, not a "single species" as asserted by the Examiner. The specification provides clear description of not only full length DNA19355 polypeptides, but soluble and variant forms thereof. For example, the definitions on pages 10 and 11 clearly describe various forms of native sequence DNA19355 polypeptide, as well as soluble, extracellular domain forms and variant forms. The specification also describes, for instance on pages 15 and 16, how such soluble and variant forms may be prepared and identified. Such disclosure will be clearly understood by those skilled in the art and demonstrate that Applicants were in "possession" of such polypeptides and the DNA sequences which encode such polypeptides.

Claims 1 and 3-9 were rejected under Section 112, first paragraph, as not being enabled for fragments comprising amino acid residues from positions 48, 49, 50...or 57 to 177. This rejection is respectfully traversed. The specification clearly teaches that native sequence, full length DNA19355 polypeptide is a Type II transmembrane molecule in the TNF family and thus comprises an intracellular domain, a transmembrane domain and an extracellular domain. The specification at page 11, lines 2-9, states that optionally, a DNA19355 extracellular domain polypeptide will comprise amino acid residues X to 177 of Fig. 1, wherein X is any one of amino acid residues 48 to 57 of Fig. 1. In Example 1, page 39 of the specification, Applicants report that hydropathy analysis of the full length molecule suggested that the transmembrane region of the polypeptide includes residues 26 to 51, and that the extracellular region includes residues 52 to 177. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain specifically mentioned (see, page 11, lines 7-9).

In Examples 4 and 5, Applicants report the results of assays showing the apoptotic activity and NF-KB activation by DNA19355 polypeptide. In those particular assays, full length forms of the DNA19355 polypeptide were tested. The testing of the full length form of the polypeptide as opposed to a soluble, extracellular domain form of the polypeptide, however, does not preclude one skilled in the art from understanding the activity or function of such a soluble, extracellular domain DNA19355 polypeptide. It is well known in the art that Type II transmembrane molecules such as DNA19355 polypeptide typically are cleaved at the cell surface and form a homotrimeric molecule which functions as a soluble cytokine (see, e.g., specification at page 5, lines 1-8). Accordingly, it is submitted that those skilled in the art will readily understand how to make and use such claimed "fragments" as the specification clearly provides that such fragments represent various soluble forms of the extracellular domain of DNA19355 polypeptide. Further, experimental testing of soluble constructs which included the DNA19355 polypeptide ECD (comprising residues 52 to 177) showed that its' activities include binding to the GITR receptor and stimulation of TNF-alpha by T cells (see

Examples 12 and 14, pages 48-51 of specification).

Section 102 Rejections

Claims 1 and 3-9 were rejected under Section 102(e) as being anticipated by Yu et al. (US Patent 5,998,171). For the reasons below, Applicants respectfully traverse the rejection.

The Yu et al. patent cannot anticipate claims 1 or 3-9 (or the claims added by way of amendment above) under Section 102 because the Yu et al. patent disclosure is non-enabling. The Yu et al. patent describes a polypeptide (and its' encoding DNA) called "endokine alpha". The patent discloses that the endokine alpha polypeptide is a purported member of the TNF family of cytokines, and specifically states that when its' sequence is aligned with that of human TNF-alpha, the endokine alpha polypeptide is about 30% similar and about 22% identical to human TNF-alpha. (Yu et al. Patent at Col. 6, lines 63-65; see also, Col. 5, lines 35-40; Figure 2).

Although the Yu et al. patent provides such structural information concerning endokine alpha, it fails to teach one of ordinary skill how to use such an endokine alpha polypeptide (or a DNA encoding it). The patent provides no functional data to suggest how the endokine alpha polypeptide or its' DNA may be used. Instead, the Yu et al. patent disclosure merely contains generic statements that the endokine alpha polypeptide can be tested in cytotoxity or proliferation assays (see, e.g., Col. 11, lines 55-64) or that its' nucleic acid may be utilized as a hybridization probe or PCR primer (see, e.g., Col. 11, lines 35-40). The only experimental data in the patent are the results of a Northern blot assay which revealed that the gene encoding endokine alpha was detected in human brain striatum and pancreas tissue. (Yu et al. Patent, Col. 36, lines 14-16).

The Yu et al. patent disclosure falls significantly short of meeting the requirements of either Section 112 or Section 101. Yu et al. attempt to "impute" the activity or use of endokine alpha by means of homology of the molecule to another known protein, TNF-alpha. Applicants submit that such an attempt to impute activity or use must fail for a number of reasons. First, the TNF family includes a relatively large number of

molecules, and the homology of the endokine alpha polypeptide to TNF-alpha is relatively low. As mentioned above, Yu et al. report that endokine alpha polypeptide is only about 30% similar and only about 22% identical to human TNF-alpha. Furthermore, TNF-alpha is a polypeptide which has been characterized in the art as having a variety of different activities and properties. Indeed, in Col. 1, lines 27-54, Yu et al. admit that TNF is a "regulatory cytokine with pleiotropic activities" and then provide a "laundry list" of such activities. Applicants respectfully assert that until the endokine alpha had been analyzed for a function, it could simply not be predicted by the skilled artisan what the molecule could be used for or how it could be used. In this regard, the results obtained in the Northern blot analysis by Yu et al. clearly do not provide sufficient guidance to those skilled in the art what, if any, function the endokine alpha may possess, or if any such function would correlate with any of those in the laundry list of activities attributed to TNF-alpha.

Those skilled in the art would clearly not be able to understand or predict from the disclosure in the Yu et al. patent what the use(s) of endokine alpha is, much less how to use endokine alpha. Accordingly, it is believed that the Yu et al. patent is non-enabling for such polypeptide sequences and non-enabling for DNA encoding the polypeptides.

Respectfully submitted,

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Date: December 6, 2000

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ATTACHMENT A

1. An isolated nucleic acid comprising DNA encoding a DNA19355 polypeptide consisting of amino acid residues X to 177 of Fig. 1 (SEQ ID NO:1), wherein X is any one of amino acid residues 48 to 57 of Fig. 1 (SEQ ID NO:1).

2. The nucleic acid of claim 1 comprising DNA encoding a DNA19355 polypeptide consisting of amino acid residues 52 to 177 of Fig. 1 (SEQ ID NO:1).

3. A vector comprising the nucleic acid of claim 1 or claim 2.

4. The vector of claim 3 operably linked to control sequences recognized by a host cell transformed with the vector.

5. A host cell comprising the vector of claim 3.

6. The host cell of claim 5 wherein said cell is a CHO cell.

7. The host cell of claim 5 wherein said cell is an *E. coli*.

8. The host cell of claim 5 wherein said cell is a yeast cell.

9. A process for producing DNA19355 polypeptides comprising culturing the host cell of claim 5 under conditions suitable for expression of the DNA19355 polypeptide and recovering the DNA19355 polypeptide from the cell culture.

27. An isolated nucleic acid comprising a DNA encoding a polypeptide having at least 80% amino acid sequence identity with native sequence DNA19355 polypeptide consisting of amino acid residues 1 to 177 of Fig. 1 (SEQ ID NO:1), wherein said encoded polypeptide induces apoptosis in a mammalian cell.

28. The nucleic acid of claim 27 wherein said DNA encodes a polypeptide having at least 90% amino acid sequence identity with native sequence DNA19355 polypeptide consisting of amino acid residues 1 to 177 of Fig. 1 (SEQ ID NO:1).

29. The nucleic acid of claim 27 wherein said DNA encodes a polypeptide having at least 95% amino acid sequence identity with native sequence DNA19355 polypeptide consisting of amino acid residues 1 to 177 of Fig. 1 (SEQ ID NO:1).

30. A vector comprising the nucleic acid of claim 27.

31. The vector of claim 30 operably linked to control sequences recognized by a host cell transformed with the vector.

32. A host cell comprising the vector of claim 31.

33. The host cell of claim 32 which is a CHO cell.

34. The host cell of claim 32 which is an *E. coli*.

35. The host cell of claim 32 which is a yeast cell.

36. A process for producing DNA19355 polypeptides comprising culturing the host cell of claim 32 under conditions suitable for expression of the polypeptide and recovering the polypeptide from the cell culture.

37. An isolated nucleic acid comprising a DNA encoding a polypeptide having at least 80% amino acid sequence identity with native sequence DNA19355 polypeptide consisting of amino acid residues 1 to 177 of Fig. 1 (SEQ ID NO:1), wherein said encoded polypeptide activates NF-KB in a mammalian cell.

38. The nucleic acid of claim 37 wherein said encoded polypeptide has at least 90% amino acid sequence identity.

39. The nucleic acid of claim 37 wherein said encoded polypeptide has at least 95% amino acid sequence identity.

40. A vector comprising the nucleic acid of claim 37.

41. The vector of claim 40 operably linked to control sequences recognized by a host cell transformed with the vector.

42. A host cell comprising the vector of claim 41.

43. The host cell of claim 42 which is a CHO cell.

44. The host cell of claim 42 which is an *E. coli*.

45. The host cell of claim 42 which is a yeast cell.

46. A process for producing DNA19355 polypeptides comprising culturing the host cell of claim 42 under conditions suitable for expression of the polypeptide and recovering the polypeptide from the cell culture.

47. An isolated nucleic acid comprising a DNA encoding a soluble polypeptide having at least 80% amino acid sequence identity with the extracellular domain sequence of a DNA19355 polypeptide consisting of amino acid residues 52 to 177 of Fig. 1 (SEQ ID NO:1), wherein said encoded soluble polypeptide can bind GITR receptor or stimulate mammalian T cells to secrete TNF-alpha.

48. The nucleic acid of claim 47 wherein said encoded polypeptide has at least 90% amino acid sequence identity.

49. The nucleic acid of claim 48 wherein said encoded polypeptide has at least 95% amino acid sequence identity.

50. An isolated nucleic acid comprising DNA encoding (a) a DNA19355 polypeptide consisting of amino acid residues 1 to 177 of Fig. 1 (SEQ

ID NO:1) or (b) a fragment of (a) which can induce apoptosis in a mammalian cell, activate NF-KB in a mammalian cell, bind to GITR receptor or stimulate mammalian T cells to secrete TNF-alpha.

51. An isolated nucleic acid comprising DNA encoding a DNA19355 polypeptide consisting of amino acid residues 1 to 177 of Fig. 1 (SEQ ID NO:1).

52. A vector comprising the nucleic acid of claim 51.

53. The vector of claim 52 operably linked to control sequences recognized by a host cell transformed with the vector.

54. A host cell comprising the vector of claim 53.

55. The host cell of claim 54 which is a CHO cell.

56. The host cell of claim 54 which is an *E. coli*.

57. The host cell of claim 54 which is a yeast cell.

58. A process for producing DNA19355 polypeptides comprising culturing the host cell of claim 54 under conditions suitable for expression of the polypeptide and recovering the polypeptide from the cell culture.

59. An isolated nucleic acid comprising the cDNA insert of the vector deposited as ATCC accession number 209466.